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Docket Number: 28111/32975

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Thompson, et al.
Serial No. : 08/571,755
Examiner : Phillip Gambel
Art Unit : 1644
Filed : December 13, 1995
For : SPECIFIC BINDING MEMBERS FOR HUMAN
TRANSFORMING GROWTH FACTOR BETA:
MATERIALS AND METHODS

DRAFT
DECLARATION OF BRUCE L. ROBERTS

I, Bruce L. Roberts, do hereby declare and state as follows.

1. I currently hold the position of Vice President, Applied Genomics at Genzyme Molecular Oncology, a division of Genzyme Corporation. I have worked in the area of protein engineering and molecular biology for over twenty years. In particular, from 1989 to 1995, I held the position of Senior Staff Scientist at Protein Engineering Corporation (now Dyax), where I was involved in studying the display and selection via panning of protease inhibitors and CD4 variants on the surface of M13 filamentous phage. I hold a B.Sc. in Biochemistry from Carleton University, and a Ph.D. in Protein Chemistry from the University of Ottawa. A copy of my curriculum vitae is attached as Exhibit 1.

2. I have reviewed the specification and pending claims of the above-identified patent application. A copy of those claims is attached hereto as Exhibit B. I have also reviewed the Office Actions dated October 28, 1997; June 23, 1998; January 14, 1999; October 14, 1999, April 19, 2000, and November 15, 2000, along with applicants' responses thereto. I understand that claims 49 and 51-54 were rejected under 35 U.S.C. S103(a) as being obvious over Lucas et al., *J. Immunol.* 145:1415-22 (1990)

("Lucas") and/or over Dasch et al. (U.S. Patent 5,571,714; "Dasch"), in view of Marks et al., *J. Mol. Biol.* 222:581-597 (1991) ("Marks") and Iwata et al., (U.S. Patent 5,262,319, "Iwata") as evidenced by Engleman (US Patent 4,634,666, "Engleman"), Kaluza (US Patent 5,614,367, "Kaluza") and Queen (US Patent 5,585,089, "Queen"). More specifically, I understand that the Examiner asserts that Marks "state[s] that the phage display library can be used to isolate human antibodies against any antigen, by-passing hybridoma technology and immunization" (November 15, 2000 Office Action, page 3). I further understand that, based on that assertion, the Examiner has concluded that the ordinary artisan would have had a reasonable expectation of success in producing human antibodies against human TGF- β .

3. I make this Declaration specifically to address the teachings of Marks. As of the December 2, 1992 priority date of this application, neither Marks alone nor Marks in combination with the teachings then available in the art would have provided the ordinarily skilled artisan with a reasonable expectation of producing the monoclonal antibodies of the pending claims, i.e., human monoclonal antibodies that bind to human TGF- β .

4. Marks refers to the isolation of human antibodies from phage display libraries of human immunoglobulin heavy and light chain variable genes. In particular, after four rounds of rescue-selection-infection, rare phage were identified with "antigen-binding" activity directed against turkey egg-white lysozyme, bovine serum albumin or the hapten 2-phenyloxazol-5-one. None of these antigens is a human or "self" antigen. Rather, they are all antigens which would be recognized as foreign by the human immune system. This difference between foreign and self antigens is significant. Specifically, healthy human patients should be tolerant to "self" antigens and various mechanisms exist within the body to establish this tolerance. For example, arrangements of antibody genes which result in reactivity to self antigens are deleted out of the repertoire and B cells which produce anti-self antibodies are anergized.

5. Only in the very last paragraph does Marks state that they have also isolated "specificities directed to" human blood group B (which is not an 'anti-self' specificity), human tumour necrosis factor- α , and a human monoclonal antibody (Marks page 595). However, the only support for such statement is a reference to "our unpublished results." No further results or data are provided and there is no information on the precise binding characteristics of such purported antibodies, in particular whether they are specific. There is nothing in Marks which might indicate whether or to what extent antibodies to other self-antigens are present in the library. Without such information, that single statement is entirely insufficient to allow the skilled artisan to conclude that phage display could be successfully employed to produce a human antibody which binds specifically to a given human antigen, i.e. TGF β .

6. I am not aware of any teachings in the art prior to the December 2, 1992 priority date of this application that provided a technique which the ordinarily skilled artisan would have used with a reasonable expectation of success to produce human antibodies which specifically bound to any particular human antigen.

7. More specifically, I note that the present invention is concerned with TGF β and Marks is entirely silent about this cytokine. On the basis of the Marks disclosure or the Marks disclosure in combination with the teachings then available in the art, a person of ordinary skill would have no reasonable expectation of successfully isolating a human antibody against human TGF β .

8. I hereby declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: JAN 30, 2002

Bruce L. Roberts

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EMPLOYMENT

1983-1985 Scientific Officer, Biochemistry Division, National Institute for Medical Research, London, England

1985-1987 Research Scientist, Protein Engineering Group, Integrated Genetics, Framingham, Massachusetts

1987-1988 Staff Scientist I, Transgenic Group, Integrated Genetics

1988-1989 Staff Scientist II, Head of Molecular Biology, Transgenic Group, Integrated Genetics (now Genzyme)

1989-1995 Senior Staff Scientist, Protein Engineering Corporation (now Dyax)

1995-1996 Senior Staff Scientist, Gene Therapy, Genzyme Corporation, Framingham, Massachusetts

1996-1997 Associate Director, Gene Therapy, Genzyme Corporation

1997-1999 Director, Cancer Gene Therapy, Genzyme Molecular Oncology

1999-2000 Senior Director, Cancer Gene Therapy, Genzyme Molecular Oncology

2000-present Vice President, Applied Genomics, Genzyme Molecular Oncology

EDUCATION

1974-1978 B.Sc. (Biochemistry), Carleton University, Ottawa, Canada

1978-1983 Ph.D. (Protein Chemistry) University of Ottawa, Ottawa, Canada

AWARDS AND SCHOLARSHIPS RECEIVED

University of Ottawa Entrance Scholarship (1978-1980)

Canadian National Science and Engineering Research Council Postgraduate Scholarship (1979-1982)

OTHER DISTINCTIONS

Invited Speaker-1986 Penn State Symposium on Molecular Biology: The Nucleus

Invited Speaker-1988 Virginia Polytech Symposium on Large Animal Transgenics

Invited Speaker- 1989 AgBiotech Conference, Arlington, Virginia

Invited Speaker- 1997 NMHCC on Immunotherapy of Cancer , Bethesda, MD

Invited Speaker- 1998 CHI conference on New Technologies and Applications of Vaccines, Palm Beach, Florida

Invited Speaker- 1998 IBC conference on Cancer Gene Therapy, London, UK

Invited Speaker- 1999 IIR conference on Clinical Evaluation of 2nd Generation Cancer Vaccines, London, UK

Invited Speaker-1999 IBC conference on Immunotherapy for cancer, San Diego

Invited Speaker- 2000 Sabin Institute Colloquium on Cancer Vaccines, Walker's Cay

Co-author of NIH RO1 Grant Application (No CA43186) entitled
"Mutagenesis of Papovavirus Transforming Proteins (awarded for the period 1986-1991)

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PATENTS

R.C. Ladner, S.K. Guterman, B.L. Roberts, W. Markland, A.C. Ley and R.B. Kent
Directed Evolution of Novel Binding Proteins
US Patent 5,837,500

R.C. Ladner, S.K. Guterman, B.L. Roberts, W. Markland, A.C. Ley and R.B. Kent
Directed Evolution of Novel Binding Proteins
US Patent 5,571,698

A.C. Ley, R.C. Ladner, S.K. Guterman, B.L. Roberts, W. Markland, and R.B. Kent
Engineered Human-Derived Kunitz Domains that Inhibit Human Neutrophil Elastase
US Patent 5,663,143

R.C. Ladner, S.K. Guterman, B.L. Roberts, W. Markland, A.C. Ley and R.B. Kent
Human Neutrophil Elastase and Human Cathepsin G Inhibitors (Filed 2/28/92)
Priority Date of March 1, 1991 (Filing Date of US 07/664,989)

R.C. Ladner, B.L. Roberts, A.C. Ley and R.B. Kent
Process for the Development of Binding Mini-Proteins (Filed 2/27/92)
Priority Date of March 1, 1991 (Filing Date of US 07/664,989)

R.C. Ladner, S.K. Guterman, B.L. Roberts, W. Markland, A.C. Ley, and R.B. Kent
Improved Epitope Displaying Phage (Filed 2/28/92)
Priority Date of March 1, 1991 (Filing Date of US 07/664,989)

Additional Filed Applications entitled:

Methods for Identifying Therapeutic Targets

Methods of Generating Antigen-Specific Cells and Uses Thereof

Compositions and Methods for Gene-Based Vaccines to Provoke T cell
Responses